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| APPLICATION NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO. |
| 08/719,742         | 09/25/96    | WILLIAMS              |                  |

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| 1173-003<br>EXAMINER |
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| LAZARUS WESLEY E | PAPER NUMBER<br>14 |
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1646  
 DATE MAILED:

08/20/98

This is a communication from the examiner in charge of your application.  
 COMMISSIONER OF PATENTS AND TRADEMARKS

## OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on June 01, 1998

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claims

- ☒ Claim(s) 1-53 is/are pending in the application.  
 Of the above, claim(s) 16-22, 24, 45-48 remain is/are withdrawn from consideration.  
☐ Claim(s) \_\_\_\_\_ is/are allowed.  
☒ Claim(s) 1-15, 23, 25-44 and 49-53 is/are rejected.  
☐ Claim(s) \_\_\_\_\_ is/are objected to.  
☐ Claim(s) \_\_\_\_\_ are subject to restriction or election requirement.

## Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.  
☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.  
☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.  
☐ The specification is objected to by the Examiner.  
☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).  
☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been  
☐ received.  
☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_  
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

- ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

- ☒ Notice of Reference Cited, PTO-892  
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s) \_\_\_\_\_  
☐ Interview Summary, PTO-413  
☐ Notice of Draftsperson's Patent Drawing Review, PTO-948  
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

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**DETAILED ACTION**

1. The amendment filed June 01, 1998, has been entered.
2. New rejections apply.

***Oath/Declaration***

3. The applicants, in the amendment filed June 01, 1998, claim priority under 35 USC 119(e) to provisional applications 60/005,075 filed October 11, 1995 and 60/021,540 filed July 11, 1996.

In the declaration, there is no priority claimed.

The inconsistency should be resolved.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 13-15 and 43-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for repairing epithelial cell damage, does not reasonably provide enablement for preventing epithelial cell damage. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The disclosure does not provide any guidance or example as of a method of preventing epithelial cell damage using PDGF, KGF, IGF and/or IGFBP. It is unpredictable if any of this factors,

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alone or in combination, would have a preventive effect for epithelial cell damage, at which doses, under which conditions of application, for how long and for which type of cell damage. It seems for example unpredictable if not impossible to prevent burn wounds by the claimed methods. Considering the state of the prior art, it would constitute undue experimentation to make /use the invention commensurate in scope with the claims.

6. Claims 1-8, 10-15, 23, 25-44 and 49-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-12, 25-44, 49-53 are indefinite, because claim 1 recites a polypeptide having the biological activity of PDGF and a polypeptide having the biological activity of KGF, and it is not clear what the metes and bounds of the claim are. Even though the applicants define the biological activities of the growth factors, starting page 8, line 26, and exemplify what these molecules can be, there are other growth factors or molecules having the same biological activities of stimulating the growth of cells in the dermis, like members of the EGF or FGF family (see Martin et al., Progress in growth factor research 4:25-44, 1992, starting last paragraph of page 27), and therefore what is encompassed by "a polypeptide having the biological activity of PDGF" or of KGF is not clear.

Claims 3, 7, 25, 27, 30, 32 are indefinite because they recite a biologically active fragment or the biological activity of a growth factor

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Claims 25 and 27 depend on claim 1, which recites a first and a second polypeptide. Claims 25 and 27 recite respectively a third polynucleotide and a fourth polynucleotide. From the following claims, it seems that this was a typographical error and that applicants meant a third and a fourth polypeptide. Applicants is reminded that methods of repairing epithelial cell damage with DNA have not been elected by original presentation.

Claim 23 is indefinite, because it is not clear what is meant by a "package". A package is not a container, and the specification does not define a package.

***Claim Rejections - 35 USC § 102***

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 1-2, 4-6, 8-12, 13-15 are rejected under 35 U.S.C. 102(a) as being anticipated by Ring et al., Growth factors in Porcine full and partial thickness burn repair, Wound repair and regeneration, Fifth annual meeting of the wound healing society, Minneapolis, MN April 27-30, 1995, issue of January-March 1995.

Ring et al. teach a combination of rPDGF and rKGF that results in a significant increase in new epithelial area in the treatment of burns. The limitations of the claims are met.

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*Claim Rejections - 35 USC § 103*

9. Claims 3, 7, 23, 25-44 and 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ring et al., Growth factors in Porcine full and partial thickness burn repair, Wound repair and regeneration, Fifth annual meeting of the wound healing society, Minneapolis, MN April 27-30, 1995, issue of January-March 1995, cited by applicants, in view of Martin et al., Progress in growth factor research 4:25-44, 1992, Antoniades et al., US Patent 4,861,757, Gospodarowicz et al., US Patent 5,677,278, Jyung et al., Surgery 115(2):233-9, February 1994 (W) and Yanni, US Patent No 5,624,893 (A) .

Ring et al. teach a combination of rPDGF and rKGF that results in a significant increase in new epithelial area in the treatment of burns.

Martin et al. teach the effects of various growth factors in cutaneous wound repairs. He teaches that PDGF might only act in synergy with other growth factors to enhance wound healing (page 33, last paragraph). Martin also teaches that KGF acts in normal epithelial proliferation (page 31, end of first paragraph).

Antoniades et al. teach a method for healing an external wound comprising applying a composition that comprises PDGF and IGF-I.(col.4, lines 33-35 and 55-61).

Gospodarowicz et al. teach a truncated KGF, named KGF des1-23, and a pharmaceutical composition for wound healing, and teaches that KGF des1-23 has at least twice the mitogenic activity of full length KGF(col.24, lines 25-30).

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Jyung et al.(W) teach that the combination of IGF-I with IGFBP-I has a potent effect on wound healing in rats (Table 1).

Yanni teaches compositions and methods for treating corneal haze due for example to scar formation (col.7, lines 42-47 and col.4, lines 26-38) or altered wound healing (col.8, lines 52-56). These compositions comprise wound healing modulators including growth factors such as PDGF-BB, PDGF-AA, PDGF-AB, KGF, IGF-I and IGF-II (col.7, lines 42-47). The factors can be isolated from mammalian cell types or can be produced by genetically engineered microorganisms such as bacteria and yeasts (col.5, lines 46-52). The individual wound healing modulators or combinations thereof can be applied uniquely or sequentially. They can be applied topically, in various forms, like solutions, gels, or via a solid matrix (col.11, lines 1-20).

It would have been obvious for one of skill in the art at the time of the invention, to modify the teachings of Ring that shows the effect of PDGF+KGF in wound healing by adding other growth factors as suggested by Martin who teaches that PDGF acts in synergy with other growth factors. It would have been obvious to add other growth factors like IGF as taught by Antoniades, or IGF1+IGFBP1 as taught by Jyung, or KGFdes1-23 as taught by Gospodarowicz, in order to improve wound healing. One would have been motivated to do so, and one would have had reasonable expectation of success, because of the positive results obtained with the combinations of for example PDGF and KGF, or PDGF and IGF. Furthermore, one would have been motivated to

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use a combination of PDGF and other growth factors like recited by Yanni, in order to obtain even better wound healing.

10. Claims 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ring et al., Growth factors in Porcine full and partial thickness burn repair, Wound repair and regeneration, Fifth annual meeting of the wound healing society, Minneapolis, MN April 27-30, 1995, issue of January-March 1995, cited by applicants, in view of Martin et al., Progress in growth factor research 4:25-44, 1992, Antoniadis et al., US Patent 4,861,757, Gospodarowicz et al., US Patent 5,677,278, Jyung et al., Surgery 115(2):233-9, February 1994 (W). and Yanni, US Patent No 5,624,893 (A), as recited for claims above, and further in view of Song et al., US Patent 5,399,361.

The teachings of Ring, Martin, Antoniadis, Gospodarowicz and Jyung have been discussed above. They do not teach a pharmaceutical composition, like for example a sponge.

Song teaches sponges used for enhancing wound healing, that comprises various growth factors, including PDGF, KGF, IGF-1 and IGF-2 (col.2, lines 46-49).

It would have been obvious for one skilled in the art at the time of the invention, to use sponges as taught by Song, with growth factors known for their wound healing effects as discussed earlier, for enhancing wound healing.

11. Applicants arguments have been fully considered but are moot in view of the new rejections.

12. No claim is allowed.

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13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eliane Lazar-Wesley, PhD, whose telephone number is (703) 305 4059. The examiner can normally be reached on Monday-Friday from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731.

Official papers filed by fax should be directed to (703) 308 4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

EW

ELW

August 13, 1998

  
LORRAINE SPECTOR  
PRIMARY EXAMINER